

Experiment Number: K06898

Route: Gavage, IV

Species/Strain: Mice/B6C3F1

Toxicokinetics Data Summary

Compound: alpha-Thujone/ Analyte: alpha-Thujone

CAS Number: 546-80-5

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Battelle Columbus

Male

Treatment Group (mg/kg)

3.2 IV Plasma<sup>d</sup>

40 Gavage Plasma<sup>b,e</sup>

80 Gavage Plasma<sup>c,e</sup>

	3.2 IV Plasma <sup>d</sup>	40 Gavage Plasma <sup>b,e</sup>	80 Gavage Plasma <sup>c,e</sup>
C <sub>0min</sub> _pred (ng/mL)	676 ± 92		
C <sub>max</sub> _pred (ng/mL)		228 ± 86	544 ± 197
T <sub>max</sub> _pred (minute)		5.26 ± 5.76	6.59 ± 2.58
C <sub>max</sub> _obs (ng/g)		571 ± 497	2200 ± 600
T <sub>max</sub> _obs (minute)		5.00 ± 0.00	5.00 ± 0.00
k <sub>01</sub> (minute <sup>-1</sup> )		0.574 ± 0.923	0.167 ± 1.92
K <sub>01</sub> Half-life (minute)		1.21 ± 1.94	4.15 ± 47.6
k <sub>10</sub> (minute <sup>-1</sup> )	0.0334 ± 0.0112	0.0556 ± 0.677	0.113 ± 0.006
k <sub>10</sub> Half-life (minute)	20.8 ± 7.0	12.5 ± 151	6.13 ± 0.35
Cl (mL/min)	535 ± 53		
Cl <sub>1_F</sub> (mL/min/kg)		4920 ± 1650	3290 ± 8300
V <sub>1</sub> (mL/kg)	4730 ± 640		
V <sub>1_F</sub> (mL/kg)		147000 ± 71000	59100 ± 650000
MRT (minute)	8.85 ± 0.50		
AUC <sub>0-T</sub> (ng mL <sup>-1</sup> min)		8760	35300
AUC <sub>inf</sub> _pred (ng*mL <sup>-1</sup> min)	5990 ± 590	8140 ± 2730	24300 ± 61000

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Female

Treatment Group (mg/kg)

3.2 IV Plasma<sup>d</sup>

40 Gavage Plasma<sup>b,e</sup>

80 Gavage Plasma<sup>c,e</sup>

	3.2 IV Plasma <sup>d</sup>	40 Gavage Plasma <sup>b,e</sup>	80 Gavage Plasma <sup>c,e</sup>
C <sub>0min</sub> _pred (ng/mL)	498 ± 75		
C <sub>max</sub> _pred (ng/mL)		356 ± 263	181 ± 221
T <sub>max</sub> _pred (minute)		7.44 ± 11.6	4.44 ± 11.2
C <sub>max</sub> _obs (ng/g)		480 ± 473	1710 ± 1420
T <sub>max</sub> _obs (minute)		5.00 ± 0.00	5.00 ± 0.00
k <sub>01</sub> (minute <sup>-1</sup> )		0.499 ± 1.49	0.257 ± 76.6
k <sub>01</sub> Half-life (minute)		1.39 ± 4.15	2.69 ± 802
k <sub>10</sub> (minute <sup>-1</sup> )	0.0135 ± 0.132	0.041 ± 12.2	0.151 ± 0.012
k <sub>10</sub> Half-life (minute)	4.60 ± 0.36	51.5 ± 506	16.9 ± 4900
Cl (mL/min)	969 ± 95		
Cl <sub>1_F</sub> (mL/min/kg)		1370 ± 11700	7380 ± 30400
V <sub>1</sub> (mL/kg)	6430 ± 970		
V <sub>1_F</sub> (mL/kg)		102000 ± 155000	180000 ± ND
MRT (minute)	6.64 ± 0.52		
AUC <sub>0-T</sub> (ng mL <sup>-1</sup> min)		1460	21300
AUC <sub>inf</sub> _pred (ng*mL <sup>-1</sup> min)	3300 ± 320	29200 ± 248000	10800 ± 42400

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Male

Treatment Group (mg/kg)

3.2 IV Brain<sup>a</sup>

40 Gavage Brain<sup>a</sup>

80 Gavage Brain<sup>a</sup>

	3.2 IV Brain <sup>a</sup>	40 Gavage Brain <sup>a</sup>	80 Gavage Brain <sup>a</sup>
Cmax_obs (ng/g)	1610 ± 2180	1580 ± 1500	5690 ± 865
Tmax_obs (minute)	5.67	10.7	11.3
Half-life (minute)	6.07	29.0	104
AUC_0-T (ng*g <sup>-1</sup> *min)	34800		
AUC_0-T (ng/g* min)		15400	75500
AUCinf_pred (ng*g <sup>-1</sup> *min)	34900		
AUCinf_pred (ng*mL <sup>-1</sup> min)		16700	77500

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Female

Treatment Group (mg/kg)

3.2 IV Brain<sup>a</sup>

40 Gavage Brain<sup>a</sup>

80 Gavage Brain<sup>a</sup>

	3.2 IV Brain <sup>a</sup>	40 Gavage Brain <sup>a</sup>	80 Gavage Brain <sup>a</sup>
Cmax_obs (ng/g)	2070 ± 1720	2280 ± 1250	5580 ± 4160
Tmax_obs (minute)	6.00	9.33	10.0
Half-life (minute)	4.19	50.4	37.0
AUC_0-T (ng*g <sup>-1</sup> *min)	43000		
AUC_0-T (ng/g* min)		12100	48500
AUCinf_pred (ng/g*min)	13300	48900	
AUCinf_pred (ng*g <sup>-1</sup> min)			43100

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## LEGEND

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### MODELING SOFTWARE

WinNonlin Version 5.0.1

### MODELING METHOD & BEST FIT MODEL

<sup>a</sup>WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Noncompartmental Analysis (NCA)

<sup>b</sup>WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, one-compartment with first order absorption and elimination with 1/Y<sup>2</sup> weighting (Model No. 3)

<sup>c</sup>WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, Two compartment with first order absorption and elimination with 1/Y weighting (Model No. 13)

<sup>d</sup>WinNonlin, Version 5.0.1, Pharsight Corporation, Mountain View, CA, One compartment with bolus input and first order elimination with 1/Y<sup>2</sup> weighting (Model No. 1)

### EXCEPTION

<sup>e</sup> AUC 0-T standard error of the mean, SE, was ND, not detected.

### ANALYTE

Alpha-Thujone

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TK PARAMETERS

Cmin = Fitted plasma concentration at time zero (IV only)

Cmax = Observed or Predicted Maximum plasma (or tissue) concentration

Tmax = Time at which Cmax predicted or observed occurs

Half-Life = Non-compartmental analysis (NCA) terminal elimination rate constant, NCA ke or kelim

k01 = Absorption rate constant, ka

k01 Half-life = Half-life of the absorption process to the central compartment

k10 = Elimination rate constant from the central compartment also ke or kelim

k10 Half-life = Half-life for the elimination process from the central compartment

Cl = Clearance, includes total clearance

Cl1\_F = Apparent clearance of the central compartment, also Cl\_F for gavage groups in non-compartmental model

V1 = Volume of distribution of the central compartment, includes Vd and V volume of distribution, Vz apparent volume of distribution NCA,

Vapp apparent volume of distribution for intravenous studies

V1\_F = Apparent volume of distribution for the central compartment includes Vd\_F, V\_F for oral groups, and Vc\_F

MRT = Mean Residence Time

AUC\_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast

AUCinf\_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

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## TK PARAMETERS PROTOCOL

## ANALYSIS METHOD

Target times for blood and brain collection for the intravenous phase of the study were - male rats at 5, 10, 20, and 45 minutes, and 1, 2, 4, 6, 8, and 12 hours; female rats at 5, 10, 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, and 3 hours; and male and female mice at 2, 5, 7, 10, 15, 20, 30, and 45 minutes, and 1 and 1.5 hours. Target times for blood and brain collection for the gavage phase of the study were: male and female rats at 2, 5, 10, and 30 minutes, and 1.5, 3, 6, and 12 hours; and male and female mice at 2, 5, 10, 20, and 40 minutes, and 1.5 hours, 2 hours (40 mg/kg female mice only), 3 hours, 4 hours (80 mg/kg female mice only), 5 hours (40 mg/kg male mice only), and 6 hours (80 mg/kg male mice only).

## TK\_INTRAVENOUS PLASMA

3.2 mg/kg Male and Female

Thirty animals/species/sex/compound/dosage group (excluding replacements) were given a single IV injection of a-thujone in Cremophor-ethanol-water (1,1,8) using a catheter surgically implanted by the animal supplier into the jugular vein. Dosages were administered at a volume of 2 mL/kg (rats) and 4 mL/kg (mice). Animals were weighed the morning of dosing for calculation of the dosing volume. The dosing volume was administered as a bolus push. Dosed 6/25-27/02

## TK\_GAVAGE PLASMA

40 mg/kg, 80 mg/kg Male and Female

Twenty-four (and any replacements) animals/species/sex/compound/dosage group were given a single oral gavage administration of a-thujone in 0.5 percent aqueous methylcellulose. Doses were administered at a volume of 5 mL/kg (rats) and 10 mL/kg (mice). Non-fasted animals were given a single gavage administration. Dosed 12/11-13/02

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#### TK PARAMETERS PROTOCOL (cont'd)

##### TK\_INTRAVENTOUS BRAIN

###### 3.2 mg/kg Male and Female

Thirty animals/species/sex/compound/dosage group (excluding replacements) were given a single IV injection of a-thujone in Cremophor-ethanol-water (1,1,8) using a catheter surgically implanted by the animal supplier into the jugular vein. Dosages were administered at a volume of 2 mL/kg (rats) and 4 mL/kg (mice). Animals were weighed the morning of dosing for calculation of the dosing volume. The dosing volume was administered as a bolus push. Dosed 6/25-27/02

##### TK\_GAVAGE BRAIN

###### 40 mg/kg, 80 mg/kg Male and Female

Twenty-four (and any replacements) animals/species/sex/compound/dosage group were given a single oral gavage administration of a-thujone in 0.5 percent aqueous methylcellulose. Doses were administered at a volume of 5 mL/kg (rats) and 10 mL/kg (mice). Non-fasted animals were given a single gavage administration. Dosed 12/11-13/02